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=> file hcaplus
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FILE COVERS 1907 - 25 Jan 2005  VOL 142 ISS 5
FILE LAST UPDATED: 24 Jan 2005  (20050124/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 12:32:31 ON 25 JAN 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 12:32:48 ON 25 JAN 2005
               E ALTIERI D/AU,IN
L1          124 S E5-E10
               E WEISS R/AU,IN
L2          400 S E3-E4,E15
               E WEISS ROBERT/AU,IN
L3          166 S E3-E4
               E WEISS ROBERT /AU,IN
               E WEISS ROBERT M/AU,IN
L4          101 S E3-E5
               E SMITH S,AU,IN
               E SMITH S/AU,IN
L5          648 S E3-E4,E17-E19
               E SMITH SHANNON/AU,IN
L6           18 S E3-E4,E6-E7
               E MORRIS V/AU,IN
L7            9 S E3-E5
               E MORRIS VICTOR/AU,IN
L8            4 S E3-E6
               E WHEELER M/AU,IN
L9           32 S E3-E8
               E WHEELER MARCIA/AU,IN
L10          45 S E3-E6
               E PLESCIA J/AU,IN
L11          38 S E3-E7
L12        1499 S L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR
L13         105 S L12 AND (?CANCER? OR ?NEOPLAS? OR ?TUMOR? OR MALIGNANT? OR CA
L14           2 S L13 AND (CIS OR CARCINOMA (L) IN (L) SITU)
L15          18 S L13 AND (BLADDER OR PROSTATE)
               E SURVIVIN
L16         866 S E3
L17          53 S L13 AND L16
L18          12 S L17 AND L15
               E URINE
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L19      203167 S E3
L20           5 S L17 AND L18 AND L19
L21           0 S L20 AND (NUCLEIC (L) ACID AND DNA)

     FILE 'REGISTRY' ENTERED AT 13:17:09 ON 25 JAN 2005
               E SURVIVIN
L22          85 S E3-E6

     FILE 'HCAPLUS' ENTERED AT 13:17:44 ON 25 JAN 2005
L23         545 S L22
L24          33 S L18 OR L***

     FILE 'HCAPLUS' ENTERED AT 13:45:03 ON 25 JAN 2005

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L24  ANSWER 1 OF 33  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2004:883409  HCAPLUS
DOCUMENT NUMBER:         142:4194
TITLE:                   Mitochondrial survivin inhibits apoptosis and promotes
                         tumorigenesis
AUTHOR(S):               Dohi, Takehiko; Beltrami, Elena; Wall, Nathan R.;
                         Plescia, Janet; Altieri, Dario C.
CORPORATE SOURCE:        Department of Cancer Biology and the Cancer Center,
                         University of Massachusetts Medical School, Worcester,
                         MA, USA
SOURCE:                  Journal of Clinical Investigation (2004), 114(8),
                         1117-1127
                         CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER:               American Society for Clinical Investigation
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Evasion of apoptosis is a hallmark of cancer, but the mol. circuitries of
     this process are not understood.  Here we show that survivin, a member of
     the inhibitor of apoptosis gene family that is overexpressed in cancer,
     exists in a novel mitochondrial pool in tumor cells.  In response to cell
     death stimulation, mitochondrial survivin is rapidly discharged in the
     cytosol, where it prevents caspase activation and inhibits apoptosis.
     Selective targeting of survivin to mitochondria enhances colony formation
     in soft agar, accelerates tumor growth in immuno-compromised animals, and
     abolishes tumor cell apoptosis in vivo.  Therefore, mitochondrial survivin
     orchestrates a novel pathway of apoptosis inhibition, which contributes to
     tumor progression.
IT   371761-91-0
     RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
     unclassified); BIOL (Biological study)
        (mitochondrial survivin inhibits apoptosis and promotes tumorigenesis
        in human cancer cells)
REFERENCE COUNT:         40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24  ANSWER 2 OF 33  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2004:693438  HCAPLUS
DOCUMENT NUMBER:         141:188545
TITLE:                   An IAP-IAP Complex Inhibits Apoptosis
AUTHOR(S):               Dohi, Takehiko; Okada, Kazuya; Xia, Fang; Wilford,
                         Casey E.; Samuel, Temesgen; Welsh, Kate; Marusawa,
                         Hiroyouki; Zou, Hua; Armstrong, Robert; Matsuzawa,
                         Shu-ichi; Salvesen, Guy S.; Reed, John C.;
                         Altieri, Dario C.
CORPORATE SOURCE:        Department of Cancer Biology and the Cancer Center,
                         University of Massachusetts Medical School, Worcester,
                         MA, 01605, USA
```

SOURCE: Journal of Biological Chemistry (2004), 279(33), 34087-34090
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Regulators of apoptosis are thought to work in concert, but the mol. interactions of this process are not understood. Here, we show that in response to cell death stimulation, survivin, a member of the inhibitor of apoptosis (IAP) gene family, assocs. with another IAP protein, XIAP, via conserved baculovirus IAP repeats. Formation of a survivin-XIAP complex promotes increased XIAP stability against ubiquitination/proteasomal destruction and synergistic inhibition of apoptosis, which is abolished in XIAP-/- cells. Therefore, orchestration of an IAP-IAP complex regulates apoptosis.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(survivin-XIAP complex promotes increased XIAP stability against ubiquitin/proteasome and synergistic inhibition of apoptosis in human lymphoblastoid and kidney cells, and breast carcinoma cells)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:533790 HCAPLUS
DOCUMENT NUMBER: 141:67288
TITLE: Detection of **survivin** in the biological fluids of **cancer** patients
INVENTOR(S): **Altieri, Dario C.; Weiss, Robert M. ; Smith, Shannon D.; Wheeler, Marcia A.; Morris, Victor A.; Plescia, Janet**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 42,302.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004126775	A1	20040701	US 2003-463867	20030618
US 2002160395	A1	20021031	US 2002-42302	20020111
WO 2004112570	A2	20041229	WO 2004-US18187	20040610

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2001-260898P	P	20010112
US 2002-42302	A2	20020111
US 2003-463867	A	20030618

AB The present invention includes a method for diagnosing **cancer** and predicting recurrent **cancer** comprising detecting the

presence of **survivin** in the biol. fluid of a patient. The present invention also provides kits comprising one or more agents that detect **survivin** polypeptide or **survivin** nucleic acid and a container for collecting biol. fluid for testing.

IT **371761-91-0, Survivin**
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(detection of **survivin** in biol. fluids of **cancer** patients)

L24 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:516835 HCAPLUS
DOCUMENT NUMBER: 141:154649
TITLE: Coupling apoptosis resistance to the cellular stress response: The IAP-Hsp90 connection in cancer
AUTHOR(S): **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Cell Cycle (2004), 3(3), 255-256
CODEN: CCEYAS; ISSN: 1538-4101
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Understanding how tumor cells manage to survive and proliferate in ever-changing and often harmful microenvironments is a daunting challenge in tumor biol., and a major cause of treatment failure in the oncol. clinic. Recent data have now demonstrated a direct link between the mol. chaperone Hsp90 and survivin, a dual regulator of cell proliferation and cell death over-expressed in virtually every human tumor. While the survivin-Hsp90 association may help tumor cells elevate their anti-apoptotic threshold and promote their proliferation, it may also provide new opportunities for rational cancer therapy.

IT **371761-91-0**, Survivin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(coupling apoptosis resistance to cellular stress response and IAP-Hsp90 connection in cancer)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:93873 HCAPLUS
DOCUMENT NUMBER: 140:144393
TITLE: IL-11 protects human microvascular endothelium from alloinjury in vivo by induction of survivin expression
AUTHOR(S): Kirkiles-Smith, Nancy C.; Mahboubi, Keyvan; **Plescia, Janet**; McNiff, Jennifer M.; Karras, James; Schechner, Jeffrey S.; **Altieri, Dario C.**; Pober, Jordan S.
CORPORATE SOURCE: Interdepartmental Program in Vascular Biology and Transplantation, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06510, USA
SOURCE: Journal of Immunology (2004), 172(3), 1391-1396
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB IL-11 can reduce tissue injury in animal models of inflammation but the mechanism(s) is unknown. When C.B-17 SCID/beige mice bearing human skin grafts are injected i.p. with human PBMC allogeneic to the donor skin, infiltrating T cells destroy human microvessels by day 21. Intradermal

injection of human IL-11 (500 ng/day) delays the time course of graft microvessel loss without reducing the extent of T cell infiltration. Protective actions of IL-11 are most pronounced on day 15. IL-11 has no effect on T cell activation marker, effector mol., cytokine expression, or endothelial ICAM-1 expression. IL-11 up-regulates the expression of survivin, a cytoprotective protein, in graft keratinocytes and endothelial cells. Topical application of survivin antisense oligonucleotide down-regulates survivin expression in both cell types and largely abrogates the protective effect of IL-11. The authors conclude that in this human transplant model, IL-11 exerts a cytoprotective rather than anti-inflammatory or immunomodulatory effect mediated through induction of survivin.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin-11 protects human microvascular endothelium from alloinjury by induction of survivin expression)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:26016 HCAPLUS
DOCUMENT NUMBER: 140:91734
TITLE: Acute Ablation of Survivin Uncovers p53-dependent Mitotic Checkpoint Functions and Control of Mitochondrial Apoptosis
AUTHOR(S): Beltrami, Elena; **Plescia, Janet**; Wilkinson, John C.; Duckett, Colin S.; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Journal of Biological Chemistry (2004), 279(3), 2077-2084
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Survivin is a member of the Inhibitor of Apoptosis gene family that has been implicated in cell division and suppression of apoptosis. Here, we show that preferential ablation of the nuclear pool of survivin by RNA interference produces a mitotic arrest followed by re-entry into the cell cycle and polyploidy. Survivin ablation causes multiple centrosomal defects, aberrant multi-polar spindle formation, and chromatin missegregation, and these phenotypes are exacerbated by loss of the cell cycle regulator, p21Waf1/Cip1 in p21-/- cells. The mitotic checkpoint activated by loss of survivin is mediated by induction of p53 and associated with increased expression of its downstream target, p21Waf1/Cip1. Accordingly, p53-/- cells exhibit reduced mitotic arrest and enhanced polyploidy upon survivin ablation as compared with their p53+/+ counterparts. Partial reduction of the cytosolic pool of survivin by RNA interference sensitizes cells to UV B-mediated apoptosis and results in enhanced caspase-9 proteolytic cleavage, whereas complete ablation of cytosolic survivin causes loss of mitochondrial membrane potential and spontaneous apoptosis. These data demonstrate that survivin has separable checkpoint functions at multiple phases of mitosis, and in the control of mitochondrial-dependent apoptosis.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(acute ablation of survivin uncovers p53-dependent mitotic checkpoint functions and control of mitochondrial apoptosis in human tumor cells)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1009872 HCAPLUS
DOCUMENT NUMBER: 140:234238
TITLE: Full-Length Dominant-Negative **Survivin** for **Cancer** Immunotherapy
AUTHOR(S): Pisarev, Vladimir; Yu, Bin; Salup, Raoul; Sherman, Simon; **Altieri, Dario C.**; Gabrilovich, Dmitry I.
CORPORATE SOURCE: University of Nebraska Medical Center Eppley Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA
SOURCE: Clinical Cancer Research (2003), 9(17), 6523-6533
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PURPOSE: The goal of this study is to investigate the possible utility of dendritic cells (DCs) transduced with the human full-length dominant-neg. **survivin** for **cancer** immunotherapy. Exptl. Design: Mononuclear cells were collected from HLA-A2-pos. healthy volunteers and patients with **prostate cancer.** DCs were transduced with an adenoviral vector containing a full-length, dominant-neg. **survivin** gene. After three rounds of stimulation, the T-cell response against three different **survivin**-derived HLA-A2-matching peptides was tested in IFN-γ enzyme-linked immunospot and CTL assays. RESULTS: Seven of eight healthy volunteers and **cancer** patients showed a significant response to at least two different **survivin**-derived epitopes in the enzyme-linked immunospot assay. One patient responded to only one peptide. All four healthy volunteers and two of three patients tested demonstrated a specific CTL response against T2 target cells loaded with one **survivin**-derived epitope. Two donors and two patients had a significant CTL response against two different epitopes. Significant cytotoxic activity was seen against HLA-A2-pos. MCF-7 **tumor** cells that express **survivin.** That response was specific for **survivin** and was MHC class I restricted. Because **survivin** is expressed in CD34+ hematopoietic progenitor cells (HPCs), we tested whether the antisurvivin CTLs can recognize normal HPCs. The incubation of **survivin**-specific CTLs with CD34+ cells did not significantly decrease the colony-forming ability of HPCs. CONCLUSIONS: DCs transduced with dominant-neg. **survivin** induce potent **survivin** -specific CTL responses able to recognize and kill **tumor** cells. This response does not significantly affect HPCs. Thus, this study may provide rationale for immunotherapeutic clin. trials using a DC vaccine transduced with the dominant-neg. **survivin.**
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(full-length dominant-neg. **survivin** for **cancer** immunotherapy)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 8 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:980276 HCAPLUS
DOCUMENT NUMBER: 140:318954
TITLE: Survivin expression in oral squamous cell carcinoma
AUTHOR(S): Lo Muzio, L.; Pannone, G.; Staibano, S.; Mignogna, M. D.; Rubini, C.; Mariggio, M. A.; Procaccini, M.; Ferrari, F.; De Rosa, G.; **Altieri, D. C.**
CORPORATE SOURCE: Faculty of Medicine, Institute of Dental Sciences, University of Ancona, Ancona, Italy
SOURCE: British Journal of Cancer (2003), 89(12), 2244-2248
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 110 cases of oral squamous cell carcinoma (SCC) together with six lymph node and one distant metastatic lesions was analyzed for expression of survivin, a recent apoptosis inhibitor, by immunohistochem. and Western blotting. In total, 91 cases (82.7%) of carcinoma and all metastasis (seven cases, 100%) were pos. for survivin expression, with weighted survivin scores ranging from 1 to 4. In contrast, normal oral epithelium did not express survivin. There was no significant correlation between survivin expression and age, sex, tumor size, the presence of lymph node and distant metastases. Survivin expression was increased in poorly differentiated tumors, even if differences were not statistically significant. In contrast, when analyzed for prognostic significance, patients with low survivin expression had statistically significant better survival rates than the group with high survivin expression ($P<0.05$). These data suggest that survivin expression may identify cases of oral SCC with more aggressive and invasive phenotype.
IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(survivin expression and prognostic significance in oral squamous cell carcinoma)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:970956 HCAPLUS
DOCUMENT NUMBER: 140:57482
TITLE: Fibronectin Protects **Prostate Cancer** Cells from **Tumor** Necrosis Factor-α-induced Apoptosis via the AKT/ **Survivin** Pathway
AUTHOR(S): Fornaro, Mara; **Plescia, Janet**; Chheang, Sophie; Tallini, Giovanni; Zhu, Yong-M.; King, Michael; **Altieri, Dario C.**; Languino, Lucia R.
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Journal of Biological Chemistry (2003), 278(50), 50402-50411
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Integrins are cell surface heterodimeric transmembrane receptors that, in addition to mediating cell adhesion to extracellular matrix proteins modulate cell survival. This mechanism may be exploited in **cancer** where evasion from apoptosis invariably contributes to cellular transformation. The mol. mechanisms responsible for matrix-induced survival signals begin to be elucidated. Here we report that the inhibitor of apoptosis **survivin** is expressed in vitro in human **prostate** cell lines with the highest levels present in aggressive **prostate cancer** cells such as PC3 and LNCaP-LN3 as well as in vivo in prostatic adenocarcinoma. We also show that interference with **survivin** in PC3 **prostate cancer** cells using a Cys84→Ala dominant neg. mutant or **survivin** antisense cDNA causes nuclear fragmentation, hypo-diploidy, cleavage of a 32-kDa pro-form caspase-3 to active caspase-3, and proteolysis of the caspase substrate poly(ADP-ribose) polymerase. We demonstrate that in the aggressive PC3 cell line, adhesion to fibronectin via β1 integrins results in

up-regulation of **survivin** and protection from apoptosis induced by **tumor** necrosis factor-α (TNF-α). In contrast, **survivin** is not up-regulated by cell adhesion in the non-**tumorigenic** LNCaP cell line. Dominant neg. **survivin** counteracts the ability of fibronectin to protect cells from undergoing apoptosis, whereas wild-type **survivin** protects non-adherent cells from TNF-α-induced apoptosis. Evidence is provided that expression of β1A integrin is necessary to protect non-adherent cells transduced with **survivin** from TNF-α-induced apoptosis. In contrast, the β1C integrin, which contains a variant cytoplasmic domain, is not able to prevent apoptosis induced by TNF-α in non-adherent cells transduced with **survivin.** Finally, we show that regulation of **survivin** levels by integrins are mediated by protein kinase B/AKT. These findings indicate that **survivin** is required to maintain a critical anti-apoptotic threshold in **prostate cancer** cells and identify integrin signaling as a crucial survival pathway against death receptor-mediated apoptosis.

IT **371761-91-0**, Proteinase inhibitor, **survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AKT/**survivin** pathway; fibronectin protects **prostate cancer** cells from **tumor** necrosis factor-α-induced apoptosis via the AKT/**survivin** pathway)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:955109 HCAPLUS
DOCUMENT NUMBER: 140:55281
TITLE: Regulation of survivin function by Hsp90
AUTHOR(S): Fortugno, Paola; Beltrami, Elena; **Plescia, Janet**; Fontana, Jason; Pradhan, Deepti; Marchisio, Pier Carlo; Sessa, William C.; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(24), 13791-13796
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pathways controlling cell proliferation and cell survival require flexible adaptation to environmental stresses. These mechanisms are frequently exploited in cancer, allowing tumor cells to thrive in unfavorable milieus. Here, we show that Hsp90, a mol. chaperone that is central to the cellular stress response, assocs. with survivin, an apoptosis inhibitor and essential regulator of mitosis. This interaction involves the ATPase domain of Hsp90 and the survivin baculovirus inhibitor of apoptosis repeat. Global suppression of the Hsp90 chaperone function or targeted Ab-mediated disruption of the survivin-Hsp90 complex results in proteasomal degradation of survivin, mitochondrial-dependent apoptosis, and cell cycle arrest with mitotic defects. These data link the cellular stress response to an antiapoptotic and mitotic checkpoint maintained by survivin. Targeting the survivin-Hsp90 complex may provide a rational approach for cancer therapy.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ATPase domain of Hsp90 assocs. with survivin with essential role in mitotic control and apoptosis inhibition)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:947123 HCAPLUS
DOCUMENT NUMBER: 140:91659
TITLE: Survivin, a potential early predictor of tumor progression in the oral mucosa
AUTHOR(S): Lo Muzio, L.; Pannone, G.; Leonardi, R.; Staibano, S.; Mignogna, M. D.; De Rosa, G.; Kudo, Y.; Takata, T.; **Altieri, D. C.**
CORPORATE SOURCE: Institute of Dental Sciences, Faculty of Medicine, University of Ancona, Ancona, Italy
SOURCE: Journal of Dental Research (2003), 82(11), 923-928
CODEN: JDREAF; ISSN: 0022-0345
PUBLISHER: International Association for Dental Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Survivin is a recently described apoptosis inhibitor selectively over-expressed in most tumors. Immunohistochem. was used to investigate a potential role of survivin as an early predictor of malignant transformation in precancerous and cancerous lesions of the oral cavity. Survivin was present in 10/30 cases (33%) of oral precancerous lesions without malignant progression, and in 15/16 cases (94%) of oral precancerous lesions evolved into full-blown squamous cell carcinoma. Tumors that progressed from these precancerous lesions retained widespread survivin positivity (100%). Variations among group means were highly statistically significant ($p < 0.001$). No significant correlation was found between survivin expression and the degree of dysplasia. High expression of cytoplasmic/nuclear survivin is an early event during oral carcinogenesis and may provide a useful tool for the identification of precancerous lesions at higher risk of progression into invasive carcinoma.
IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(survivin expression as early predictor of tumor progression in oral mucosa)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 12 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:917578 HCAPLUS
DOCUMENT NUMBER: 140:52593
TITLE: Survivin, versatile modulation of cell division and apoptosis in cancer
AUTHOR(S): **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Oncogene (2003), 22(53), 8581-8589
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. Survivin is a member of the inhibitor of apoptosis (IAP) gene family that has attracted attention from several viewpoints of basic and translational research. Its cell cycle-regulated expression at mitosis and association with the mitotic apparatus have been of interest to cell biologists studying faithful segregation of sister chromatids and timely separation of daughter cells. Investigators interested in mechanisms of apoptosis have found survivin an evolving challenge: while survivin inhibits apoptosis in vitro and in vivo, this pathway may be more selective as compared to cytoprotection mediated by other IAPs. Finally,

basic and translational researchers in cancer biol. have converged on survivin as a pivotal cancer gene, not simply for its sharp expression in tumors and not in normal tissues, but also for the potential exploitation of this pathway in cancer diagnosis and therapy. The objective of the present contribution is to line up current evidence and emerging concepts on the multifaceted functions of survivin in cell death and cell division, and how this pathway is being pursued for novel cancer therapeutic strategies.

IT **371761-91-0**, Survivin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(survivin, versatile modulation of cell division and apoptosis in cancer)

REFERENCE COUNT: 132 THERE ARE 132 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 13 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:564068 HCAPLUS
DOCUMENT NUMBER: 139:289993
TITLE: Survivin and molecular pathogenesis of colorectal cancer
AUTHOR(S): Kim, Paul J.; **Plescia, Janet**; Clevers, Hans; Fearon, Eric R.; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, USA
SOURCE: Lancet (2003), 362(9379), 205-209
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Colorectal cancer is thought to originate in the expansion of colonic crypt cells as a result of aberrant gene expression caused by transcription factors of the T-cell factor (TCF)/β-catenin family. Survivin is a bifunctional regulator of cell death and cell proliferation expressed during embryonic development but undetectable in healthy adult tissues and re-expressed in many cancers, including colorectal cancer. Methods: The authors investigated gene expression by promoter anal., mutagenesis, and electrophoretic mobility shift assay in colorectal cancer cells. Survivin expression in human and mouse embryonic intestine was determined by in-situ hybridization and immunohistochem. Changes in apoptosis were monitored in cell lines engineered to express stabilizing mutations in β catenin. Findings: TCF/β catenin stimulated a 6-fold to 12-fold increased expression of the survivin gene in colorectal cancer cells. Three TCF-binding elements (TBE) in the survivin promoter were occupied by nuclear factors in colorectal cancer cells, and mutagenesis of the 2 proximal TBE sites abolished survivin gene expression by 75-79%. Strongly expressed at the bottom of human and mouse embryonic intestinal crypts, expression of survivin was lost in TCF-4 knockout animals, and a TCF-4 dominant neg. mutant blocked survivin gene transcription in colorectal cancer cells. Expression of non-destructible β catenin mutants increased survivin expression and protected against UV-B-induced apoptosis. Interpretation: Stimulation of survivin expression by TCF/β catenin might impose a stem cell-like phenotype to colonic crypt epithelium coupling enhanced cell proliferation with resistance to apoptosis, and contribute to the mol. pathogenesis of colorectal cancer.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(survivin and mol. pathogenesis of colorectal cancer)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 14 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:528816 HCAPLUS
DOCUMENT NUMBER: 139:274718
TITLE: Therapeutic Targeting of the Survivin Pathway in Cancer: Initiation of Mitochondrial Apoptosis and Suppression of Tumor-associated Angiogenesis
AUTHOR(S): Blanc-Brude, Olivier P.; Mesri, Mehdi; Wall, Nathan R.; **Plescia, Janet**; Dohi, Takehiko; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Clinical Cancer Research (2003), 9(7), 2683-2692
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PURPOSE: Mol. antagonists of the inhibitor of apoptosis protein survivin have shown promise as novel anticancer strategies for triggering tumor cell apoptosis, dysregulating mitotic progression, and inhibiting tumor growth in preclin. models. However, how survivin couples to the cell death machinery has remained elusive, and the relevant cellular targets of survivin antagonists have not been completely elucidated. Exptl. Design: Human umbilical vein and dermal microvascular endothelial cells were infected with replication-deficient adenoviruses encoding survivin (pAd-Survivin), green fluorescent protein (pAd-GFP), or a phosphorylation-defective survivin Thr34 Ala (pAd-T34A) dominant neg. mutant. The effect of wild-type or mutant survivin was investigated on capillary network stability, endothelial cell viability, and caspase activation in vitro and on kinetics of tumor growth and development of angiogenesis in a breast cancer xenograft model in vivo. The cell death pathway initiated by survivin targeting was mapped with respect to cytochrome c release, changes in mitochondrial transmembrane potential, and apoptosome requirements using mouse embryonic fibroblasts deficient in Apaf-1 or caspase-9. RESULTS: Adenoviral transduction of endothelial cells with pAd-Survivin inhibited growth factor deprivation- or ceramide-induced apoptosis, reduced caspase-3 and -7 generation, and stabilized three-dimensional capillary networks in vitro. Conversely, expression of pAd-T34A caused apoptosis in umbilical vein and dermal microvascular endothelial cells and resulted in caspase-3 activity. Cell death induced by survivin targeting exhibited the hallmarks of mitochondrial-dependent apoptosis with release of cytochrome c and loss of mitochondrial transmembrane potential and was suppressed in Apaf-1 or caspase-9 knockout mouse embryonic fibroblasts. When injected in human breast cancer xenografts, pAd-T34A inhibited growth of established tumors and triggered tumor cell apoptosis in vivo. This was associated with a .apprx.60% reduction in tumor-derived blood vessels by quant. morphometry of CD31-stained tumor areas, and appearance of endothelial cell apoptosis by internucleosomal DNA fragmentation in vivo. CONCLUSIONS: Survivin functions as a novel upstream regulator of mitochondrial-dependent apoptosis, and mol. targeting of this pathway results in anticancer activity via a dual mechanism of induction of tumor cell apoptosis and suppression of angiogenesis.
IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(survivin pathway in cancer initiation of mitochondrial apoptosis and suppression of tumor-associated angiogenesis)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:506386 HCAPLUS
DOCUMENT NUMBER: 140:15256

TITLE: The role of the anti-apoptotic **survivin** gene in **bladder cancer**
AUTHOR(S): **Altieri, Dario C.; Weiss, Robert M.**
CORPORATE SOURCE: Department of Pathology, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, USA
SOURCE: Progress in Oncology (2002) 81-94
CODEN: PORNAF; ISSN: 1535-9980
PUBLISHER: Jones and Bartlett Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discusses the upregulation of the **survivin** gene that has been observed in most, if not all, human **cancer** suggesting that this is a pathway commonly used to promote the survival of **tumor** cells at various stages of **tumorigenesis** and to promote their unrestricted proliferation.
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(role of anti-apoptotic **survivin** gene in **bladder cancer**)
REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:425343 HCAPLUS
DOCUMENT NUMBER: 139:357689
TITLE: Blocking survivin to kill cancer cells
AUTHOR(S): **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, USA
SOURCE: Methods in Molecular Biology (Totowa, NJ, United States) (2003), 223(Tumor Suppressor Genes, Volume 2), 533-542
CODEN: MMBIED; ISSN: 1064-3745
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. To make an ideal drug target, an apoptosis regulator should be preferentially expressed in tumor cells but not in normal tissues, and interference with its expression/ function should be sufficient to facilitate cell death, either alone, or in combination with chemotherapeutic drugs or UV/γ-irradiation Data recently appeared in the literature suggests that the human survivin gene may fulfill both of these prerequisites. Furthermore, initial evidence in vitro and in vivo has suggested that targeting survivin may provide a viable approach to kill cancer cells selectively. This review looks at these studies.
IT **371761-91-0**, Survivin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(blocking survivin to kill cancer cells)

L24 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:376629 HCAPLUS
DOCUMENT NUMBER: 138:362659
TITLE: Enhancement of taxane-based chemotherapy by a CDK1 antagonist
INVENTOR(S): **Altieri, Dario C.**; O'Connor, Daniel S.
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003039536	A1	20030515	WO 2002-US34871		20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003125374	A1	20030703	US 2002-284490		20021031
PRIORITY APPLN. INFO.:			US 2001-331054P	P	20011107
			US 2002-394252P	P	20020709

AB The invention provides a combination therapy for inhibiting the growth of **tumor**, for treating **cancer**, and for inducing cell death. The therapy comprises the sequential administration of a taxane and a CDK1 antagonist. The invention also provides pharmaceutical compns. comprising a taxane and a CDK1 antagonist and kits comprising a taxane and CDK1 antagonist.

IT **371761-91-0**, **Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors of function of; CDK1 antagonist enhancement of taxane-based chemotherapy)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:84801 HCAPLUS
DOCUMENT NUMBER: 138:301601
TITLE: Survivin Expression in Mouse Skin Prevents Papilloma Regression and Promotes Chemical-induced Tumor Progression
AUTHOR(S): Allen, Sarah M.; Florell, Scott R.; Hanks, Adrianne N.; Alexander, April; Diedrich, Miyoung J.; **Altieri, Dario C.**; Grossman, Douglas
CORPORATE SOURCE: University of Utah, The Huntsman Cancer Institute, Salt Lake City, UT, 84112, USA
SOURCE: Cancer Research (2003), 63(3), 567-572
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Induction of cutaneous squamous cell carcinoma (SCC) in mice, by topical chemical [9,10-dimethylbenzanthracene (DMBA) and phorbol 12-myristate 13-acetate (PMA)] application, is a multistep process involving papilloma formation and progression to carcinoma. We have generated a transgenic (Tg) mouse [keratin-14 (K14)-survivin] with skin expression of survivin, an inhibitor of apoptosis expressed in most human skin cancers and premalignant lesions. K14-survivin mice were resistant to DMBA-induced keratinocyte apoptosis. To investigate the role of survivin and apoptosis in cutaneous carcinogenesis, mice were treated once topically with DMBA followed by twice weekly with PMA for 32 wk. Surprisingly, tumor formation was less frequent (31% vs. 43%) and significantly delayed (P = 0.01) in K14-survivin mice compared with non-Tg littermates. On the other hand, papilloma regression was not observed in Tg mice, whereas 20% of papillomas regressed in non-Tgs; one SCC was generated in Tg mice, whereas

none were seen in non-Tgs. To increase tumor formation and SCC in particular, a second experiment was performed with mice on a p53+/- background. Again, DMBA/PMA-induced tumor formation was less (71% vs. 89%) and significantly delayed (P = 0.02) in K14-survivin p53+/- animals compared with p53+/- non-Tgs. Papilloma regression was also not observed in Tg p53+/- mice, whereas 10% of papillomas regressed in p53+/- non-Tgs. The rate of papilloma progression to SCC was 21% in Tg p53+/- mice compared with 12% in p53+/- non-Tgs. Papillomas did not reveal significant differences in mitotic or apoptotic indexes. Survivin expression was detected in all of the tumors. These results indicate that despite a paradoxical neg. effect on tumor formation, survivin expression prevents papilloma regression and promotes conversion to SCC, consistent with its expression in most skin cancers and their precursors.

IT **371761-91-0**, Survivin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(survivin expression prevents papilloma regression and promotes conversion to cutaneous squamous cell carcinoma in mouse DMBA carcinogenesis model)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:39643 HCAPLUS
DOCUMENT NUMBER: 139:17237
TITLE: Suppression of Survivin Phosphorylation on Thr34 by Flavopiridol Enhances Tumor Cell Apoptosis
AUTHOR(S): Wall, Nathan R.; O'Connor, Daniel S.; **Plescia, Janet**; Pommier, Yves; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and Cancer Center, University of Massachusetts Medical School, Worcester, MA, USA
SOURCE: Cancer Research (2003), 63(1), 230-235
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Survivin is a member of the inhibitor of apoptosis gene family that is expressed in most human cancers and may facilitate evasion from apoptosis and aberrant mitotic progression. Here, exposure of breast carcinoma MCF-7 or cervical carcinoma HeLa cells to anticancer agents, including Adriamycin, Taxol, or UVB resulted in a 4-5-fold increased survivin expression. Changes in survivin levels after anticancer treatment did not involve modulation of survivin mRNA expression and were independent of de novo gene transcription. Conversely, inhibition of survivin phosphorylation on Thr34 by the cyclin-dependent kinase inhibitor flavopiridol resulted in loss of survivin expression, and nonphosphorylatable survivin Thr34 Ala exhibited accelerated clearance as compared with wild-type survivin. Sequential ablation of survivin phosphorylation on Thr34 enhanced tumor cell apoptosis induced by anticancer agents independently of p53 and suppressed tumor growth without toxicity in a breast cancer xenograft model in vivo. These data suggest that Thr34 phosphorylation critically regulates survivin levels in tumor cells and that sequential ablation of p34cdc2 kinase activity may remove the survivin viability checkpoint and enhance apoptosis in tumor cells.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(suppression of survivin phosphorylation on Thr34 by flavopiridol enhances tumor cell apoptosis)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:983873 HCAPLUS

DOCUMENT NUMBER: 139:16923
TITLE: Validating survivin as a cancer therapeutic target
AUTHOR(S): **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Nature Reviews Cancer (2003), 3(1), 46-54
CODEN: NRCAC4; ISSN: 1474-175X
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Acquisition of the ability to evade cellular suicide, or apoptosis, is one of the master switches that contributes to cellular transformation and, ultimately, to invasive cancer. Much has been learned about the mol. organization of apoptotic pathways and their regulators, but the identification and validation of translational targets for apoptosis-based cancer therapy has posed a great challenge. Survivin is an attractive candidate for cancer therapy, so what is its potential applicability in the clinic.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(validating survivin as a cancer therapeutic target)

REFERENCE COUNT: 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:662151 HCAPLUS
DOCUMENT NUMBER: 137:350438
TITLE: Inhibitor of apoptosis protein survivin regulates vascular injury
AUTHOR(S): Blanc-Brude, Olivier P.; Yu, Jun; Simosa, Hector; Conte, Michael S.; Sessa, William C.; **Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, USA
SOURCE: Nature Medicine (New York, NY, United States) (2002), 8(9), 987-994
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Survivin (also termed Birc5) belongs to the family of genes known as inhibitors of apoptosis, and it has been implicated in both prevention of cell death and control of mitosis. The survivin pathway is exploited in cancer, but its potential role in vascular injury is unknown. Here, we show that balloon-mediated arterial injury in rabbits resulted in expression of survivin in vascular cells. Serum or PDGF-AB stimulated survivin expression in cultured smooth-muscle cells (SMCs), which suppressed apoptosis and prevented caspase activation. Adenoviral delivery of a phosphorylation-defective survivin mutant reversed the cytoprotective effect of PDGF in SMCs without affecting mitotic progression, suppressed neointimal formation in wire-injured mouse femoral arteries, and induced vascular cell apoptosis in vivo. These data identify survivin as a critical regulator of SMC apoptosis after acute vascular injury. Disrupting the survivin pathway may provide a novel therapy to limit pathol. vessel-wall remodeling.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor of apoptosis protein survivin in regulation of vascular smooth muscle cell viability mediated by PDGF-AB in vascular injury)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:577920 HCAPLUS
DOCUMENT NUMBER: 137:276811
TITLE: A p34cdc2 survival checkpoint in **cancer**
AUTHOR(S): O'Connor, Daniel S.; Wall, Nathan R.; Porter, Andrew C. G.; **Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: Cancer Cell (2002), 2(1), 43-54
CODEN: CCAECI; ISSN: 1535-6108
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A checkpoint surveying the entry into mitosis responds to defects in spindle microtubule assembly/stability. This has been used to trigger apoptosis in **cancer** cells, but how the spindle checkpoint couples to the cell survival machinery has remained elusive. Here, we report that microtubule stabilization engenders a survival pathway that depends on elevated activity of p34cdc2 kinase and increased expression of the apoptosis inhibitor and mitotic regulator, **survivin**. Pharmacol., genetic, or mol. ablation of p34cdc2 kinase after microtubule stabilization resulted in massive apoptosis independent of p53, suppression of **tumor** growth, and indefinite survival without toxicity in mice. By ablating this survival checkpoint, inhibitors of p34cdc2 kinase could safely improve the efficacy of microtubule-stabilizing agents used to treat common **cancers**.
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(p34cdc2 kinase activity during spindle checkpoint activation results in increased **survivin** expression and mitochondria-mediated **cancer** cell viability)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:555762 HCAPLUS
DOCUMENT NUMBER: 137:121595
TITLE: Detection of **survivin** in the biological fluids of **cancer** patients
INVENTOR(S): **Altieri, Dario C.; Weiss, Robert M. ; Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet**
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057787	A2	20020725	WO 2002-US574	20020111
WO 2002057787	A3	20021219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2437305	AA	20030725	CA 2002-2437305		20020111
EP 1350114	A2	20031008	EP 2002-714720		20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004533602	T2	20041104	JP 2002-558017		20020111
PRIORITY APPLN. INFO.:			US 2001-260898P	P	20010112
			WO 2002-US574	W	20020111

AB The present invention includes a method for diagnosing **cancer** comprising detecting the presence of **survivin** in the biol. fluid of a patient. The present invention also provides kits comprising one or more agents that detect **survivin** polypeptide or **survivin** nucleic acid and a container for collecting biol. fluid for testing.

IT **371761-91-0**, **Survivin**
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(detection of **survivin** in biol. fluids of **cancer** patients)

L24 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2002:448904 HCAPLUS
DOCUMENT NUMBER:	137:153144
TITLE:	Induction and regulation of tumor necrosis factor-related apoptosis-inducing ligand/Apo-2 ligand-mediated apoptosis in renal cell carcinoma
AUTHOR(S):	Griffith, Thomas S.; Fialkov, Jonathan M.; Scott, David L.; Azuhata, Takeo; Williams, Richard D.; Wall, Nathan R.; **Altieri, Dario C.**; Sandler, Anthony D.
CORPORATE SOURCE:	Department of Urology, University of Iowa, Iowa City, IA, 52242-1089, USA
SOURCE:	Cancer Research (2002), 62(11), 3093-3099 CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER:	American Association for Cancer Research
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB The lack of effective therapy for disseminated renal cell carcinoma (RCC) has stimulated the search for novel treatments including immunotherapeutic strategies. However, poor therapeutic responses and marked toxicity associated with immunol. agents has limited their use. The tumor necrosis factor family member tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/Apo-2 ligand induces apoptosis in a variety of tumor cell types, while having little cytotoxic activity against normal cells. In this study the activation and regulation of TRAIL-induced apoptosis and TRAIL receptor expression in human RCC cell lines and pathol. specimens was examined TRAIL induced caspase-mediated apoptotic death of RCC cells with variable sensitivities among the cell lines tested. Compared with TRAIL-sensitive RCC cell lines (A-498, ACHN, and 769-P), the TRAIL-resistant RCC cell line (786-O) expressed lesser amts. of the death-inducing TRAIL receptors, and greater amts. of survivin, an inhibitor of apoptosis. Incubation of 786-O with actinomycin D increased the expression of the death-inducing TRAIL receptors and, concomitantly, decreased the intracellular levels of survivin, resulting in TRAIL-induced apoptotic death. The link between survivin and TRAIL regulation was confirmed when an increase in TRAIL resistance was observed after overexpression of survivin in the TRAIL-sensitive, survivin-neg. RCC line A-498. These findings, along with our observation that TRAIL receptors are expressed in RCC tumor tissue, suggest that TRAIL may be useful as a therapeutic agent for RCC and that survivin may partially regulate TRAIL-induced cell death.

IT **371761-91-0**, Survivin

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction and regulation of tumor necrosis factor-related apoptosis-inducing ligand/Apo-2 ligand-mediated apoptosis in renal cell carcinoma)

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:335823 HCAPLUS
DOCUMENT NUMBER: 137:61201
TITLE: Regulation of microtubule stability and mitotic progression by survivin
AUTHOR(S): Giodini, Alessandra; Kallio, Marko J.; Wall, Nathan R.; Gorbsky, Gary J.; Tognin, Simona; Marchisio, Pier Carlo; Symons, Marc; **Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Department of Pathology, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: Cancer Research (2002), 62(9), 2462-2467
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Survivin is a member of the inhibitor of apoptosis (IAP) gene family, which has been implicated in both preservation of cell viability and regulation of mitosis in cancer cells. Here, we show that HeLa cells microinjected with a polyclonal antibody to survivin exhibited delayed progression in prometaphase (31.5±6.9 min) and metaphase (126.8±73.8 min), as compared with control injected cells (prometaphase, 21.5±3.3 min; metaphase, 18.9±4.5 min; $P < 0.01$). Cells injected with the antibody to survivin displayed short mitotic spindles severely depleted of microtubules and occasionally underwent apoptosis without exiting the mitotic block or thereafter. Forced expression of survivin in HeLa cells profoundly influenced microtubule dynamics with reduction of pole-to-pole distance at metaphase (8.57±0.21 μm vs. 10.58±0.19 μm; $P < 0.0001$) and stabilization of microtubules against nocodazole-induced depolymn. in vivo. These data demonstrate that survivin functions at cell division to control microtubule stability and assembly of a normal mitotic spindle. This pathway may facilitate checkpoint evasion and promote resistance to chemotherapy in cancer.

IT **371761-91-0**, Survivin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(overexpression of survivin-mediated regulation of microtubule stability and mitotic progression in human cancer and promote resistance to chemotherapy)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:229863 HCAPLUS
DOCUMENT NUMBER: 137:138159
TITLE: **Bladder cancer** detection with urinary **survivin**, an inhibitor of apoptosis
AUTHOR(S): Sharp, Jennifer D.; Hausladen, Derek A.; Maher, M. Grey; **Wheeler, Marcia A.**; Altieri, C.; **Weiss, Robert M.**
CORPORATE SOURCE: Department of Surgery (Section of Urology) and Pathology (Boyer Center for Molecular Medicine), Yale University School of Medicine, New Haven, CT, USA
SOURCE: Frontiers in Bioscience [online computer file] (2002), 7, E36-E41
CODEN: FRBIF6; ISSN: 1093-4715

URL: http://www.bioscience.org/2002/v7/e/sharp/pdf.pdf
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. The current "gold standard" for the diagnosis of **bladder cancer** is cystoscopy and urine cytol. Cystoscopy, a naked eye assessment of the **bladder**, is invasive, uncomfortable and costly while cytol. has high specificity but low sensitivity (40-60%) particularly for low-grade lesions. Therefore, there is a need for a mol. **tumor** marker assay that is simple to perform and sensitive, particularly for low-grade lesions. By looking to the pathophysiol. of **bladder cancer**, we identified **survivin**, an inhibitor of apoptosis that is not generally expressed in fully differential adult tissue and is highly expressed in **bladder cancer**. **Survivin** is detected in whole urine of patients with TCC using a simple antibody based test. The sensitivity of **survivin** testing for new or recurrent **bladder cancer** is 100% while the specificity for other **neoplastic** and non-**neoplastic** genitourinary disease is 95%. The high sensitivity of this simple, noninvasive test is well suited to **bladder cancer**, a disease with high rates of recurrence.
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(**bladder cancer** detection with urinary **survivin**, an inhibitor of apoptosis)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:884493 HCAPLUS
DOCUMENT NUMBER: 136:399240
TITLE: The molecular basis and potential role of survivin in cancer diagnosis and therapy
AUTHOR(S): **Altieri, Dario C.**
CORPORATE SOURCE: Dept of Pathology, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, USA
SOURCE: Trends in Molecular Medicine (2001), 7(12), 542-547
CODEN: TMMRCY; ISSN: 1471-4914
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Despite its genetic complexity and multifactoriality, two processes appear almost universally compromised in cancer: the control of cell proliferation and the regulation of cell lifespan. Survivin is a recently described mol. that has been implicated in both processes, and is overexpressed in most human cancers. The exploitation of the survivin signaling pathway might provide important predictive and prognostic clues in cancer diagnosis, and offer new therapeutic alternatives for cancer treatment. Survivin has regulatory function in cell proliferation and cell death, 2 processes that are central to cancer, which offers new opportunities for cancer therapy and diagnosis.
IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(mol. basis and potential role of survivin in cancer diagnosis and therapy)
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 28 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:724802 HCAPLUS

DOCUMENT NUMBER: 136:84117
TITLE: Transgenic expression of survivin in keratinocytes counteracts UVB-induced apoptosis and cooperates with loss of p53
AUTHOR(S): Grossman, Douglas; Kim, Paul J.; Blanc-Brude, Olivier P.; Brash, Douglas E.; Tognin, Simona; Marchisio, Pier Carlo; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Dermatology, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: Journal of Clinical Investigation (2001), 108(7), 991-999
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The inhibitor of apoptosis protein survivin has been implicated in both cell cycle control and apoptosis resistance. To discriminate between these different roles, we used transgenic expression of survivin in the skin as a model for cell proliferation, differentiation, and apoptosis. Transgenic mice expressing survivin under the control of a keratin-14 promoter developed normally, without histol. abnormalities of the skin or hair, epidermal hyperplasia, or developmental abnormalities of basal or suprabasal epidermis. Keratinocyte proliferation assessed under basal conditions, or after UV-B (UVB) irradiation, or phorbol ester stimulation was unchanged in survivin transgenic mice. In contrast, survivin expression inhibited UVB-induced apoptosis in vitro and in vivo (i.e., sunburn cell formation), whereas it did not affect Fas-induced cell death. When crossed with p53 knockout mice, transgenic expression of survivin in a p53+/- background substituted for the loss of a second p53 allele and further inhibited UVB-induced apoptosis. These data provide the first in vivo evidence that survivin inhibits apoptosis and suggest that this pathway may oppose the elimination of cancerous cells by p53.

IT **371761-91-0**, Survivin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transgene; transgenic expression of survivin in keratinocytes counteracts UVB-induced apoptosis and cooperates with loss of p53)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 29 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:724801 HCAPLUS
DOCUMENT NUMBER: 136:79371
TITLE: **Cancer** gene therapy using a **survivin** mutant adenovirus
AUTHOR(S): Mesri, Mehdi; Wall, Nathan R.; Li, Jia; Kim, Richard W.; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Pathology, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: Journal of Clinical Investigation (2001), 108(7), 981-990
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have constructed a replication-deficient adenovirus encoding a nonphosphorylatable Thr34→Ala mutant of the apoptosis inhibitor **survivin** (pAd-T34A) to target **tumor** cell viability in vitro and in vivo. Infection with pAd-T34A caused spontaneous apoptosis in cell lines of breast, cervical, **prostate**, lung, and colorectal **cancer**. In contrast, pAd-T34A did not affect cell viability of proliferating normal human cells, including fibroblasts,

endothelium, or smooth muscle cells. Infection of **tumor** cells with pAd-T34A resulted in cytochrome c release from mitochondria, cleavage of approx. 46-kDa upstream caspase-9, processing of caspase-3 to the active subunits of approx. 17 and 19 kDa, and increased caspase-3 catalytic activity. When compared with chemotherapeutic regimens, pAd-T34A was as effective as taxol and considerably more effective than adriamycin in induction of **tumor** cell apoptosis and enhanced taxol-induced cell death. In three xenograft breast **cancer** models in immunodeficient mice, pAd-T34A suppressed de novo **tumor** formation, inhibited by approx. 40% the growth of established **tumors**, and reduced i.p. **tumor** dissemination. **Tumors** injected with pAd-T34A exhibited loss of proliferating cells and massive apoptosis by in situ internucleosomal DNA fragmentation. These data suggest that adenoviral targeting of the **survivin** pathway may provide a novel approach for selective **cancer** gene therapy.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cancer** gene therapy using a **survivin** mutant adenovirus)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 30 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:65575 HCAPLUS
DOCUMENT NUMBER: 135:31997
TITLE: Urine detection of **survivin** and diagnosis of **bladder cancer**
AUTHOR(S): **Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet**; Colberg, John W.; **Weiss, Robert M.; Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: JAMA, the Journal of the American Medical Association (2001), 285(3), 324-328
CODEN: JAMAAP; ISSN: 0098-7484
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Context Dysregulation of apoptosis may favor onset and progression of **cancer** and influence response to therapy. **Survivin** is an inhibitor of apoptosis that is selectively overexpressed in common human **cancers**, but not in normal tissues, and that correlates with aggressive disease and unfavorable outcomes. Objective To investigate the potential suitability of **survivin** detection in urine as a novel predictive/prognostic mol. marker of **bladder cancer.** Design, Setting, and Patients Survey of urine specimens from 5 groups: healthy volunteers (n=17) and patients with **nonneoplastic** urinary tract disease (n=30), genitourinary **cancer** (n=30), new-onset or recurrent **bladder cancer** (n=46), or treated **bladder cancer** (n=35), recruited from 2 New England urol. clinics. Main Outcome Measures Detectable **survivin** levels, analyzed by a novel detection system and confirmed by Western blot and reverse transcriptase polymerase chain reaction (RT-PCR), in urine samples of the 5 participant groups. Results **Survivin** was detected in the urine samples of all 46 patients with new or recurrent **bladder cancer** using a novel detection system (31 of 31) and RT-PCR (15 of 15) methods. **Survivin** was not detected in the urine samples of 32 of 35 patients treated for **bladder cancer** and having neg. cystoscopy results. None of the healthy volunteers or patients with **prostate**, kidney, vaginal, or cervical **cancer** had

detectable **survivin** in urine samples. Of the 30 patients with **nonneoplastic** urinary tract disease, **survivin** was detected in 3 patients who had **bladder** abnormalities noted using cystoscopy and in 1 patient with an increased **prostate**-specific antigen level. Patients with low-grade **bladder cancer** had significantly lower urine **survivin** levels than patients with **carcinoma** in situ (P=.002). Conclusions Highly sensitive and specific determination of urine **survivin** appears to provide a simple, noninvasive diagnostic test to identify patients with new or recurrent **bladder cancer.**

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 31 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:5150 HCAPLUS
DOCUMENT NUMBER: 132:217813
TITLE: Transcriptional analysis of human survivin gene expression
AUTHOR(S): Li, Fengzhi; **Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Department of Pathology, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: Biochemical Journal (1999), 344(2), 305-311
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The preservation of tissue and organ homeostasis depends on the regulated expression of genes controlling apoptosis (programmed cell death). In this study, the authors have investigated the basal transcriptional requirements of the survivin gene, an IAP (inhibitor of apoptosis) prominently up-regulated in cancer. Anal. of the 5' flanking region of the human survivin gene revealed the presence of a TATA-less promoter containing a canonical CpG island of .apprx. 250 nt, three cell cycle dependent elements, one cell cycle homol. region and numerous Sp1 sites. PCR-based anal. of human genomic DNA, digested with methylation-sensitive and -insensitive restriction enzymes, indicated that the CpG island was unmethylated in both normal and neoplastic tissues. Primer extension and S1 nuclease mapping of the human survivin gene identified two main transcription start sites at position -72 and within -57/-61 from the initiating ATG. Transfection of cervical carcinoma HeLa cells with truncated or nested survivin promoter-luciferase constructs revealed the presence of both enhancer and repressor sequences and identified a minimal promoter region within the proximal -230 nt of the human survivin gene. Unbiased mutagenesis anal. of the human survivin promoter revealed that targeting the Sp1 sequences at position -171 and -151 abolished basal transcriptional activity by .apprx. 63-82%. Electrophoretic mobility-shift assay with DNA oligonucleotides confirmed formation of a DNA-protein complex between the survivin Sp1 sequences and HeLa cell exts. in a reaction abolished by mutagenesis of the survivin Sp1 sites. These findings identify the basal transcriptional requirements of survivin gene expression.

IT **261150-38-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(nucleotide sequence; transcriptional anal. of human survivin gene expression)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 32 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:352941 HCAPLUS
DOCUMENT NUMBER: 129:52672

TITLE: **Survivin**: a protein that inhibits cellular apoptosis, the gene encoding it and the development of modulators of protein activity

INVENTOR(S): **Altieri, Dario C.**
PATENT ASSIGNEE(S): Yale University, USA; Altieri, Dario C.

SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822589	A2	19980528	WO 1997-US21880	19971120
WO 9822589	A3	19981029		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2271783	AA	19980528	CA 1997-2271783	19971120
AU 9873018	A1	19980610	AU 1998-73018	19971120
AU 736587	B2	20010802		
EP 950103	A2	19991020	EP 1997-949685	19971120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6245523	B1	20010612	US 1997-975080	19971120
JP 2002514060	T2	20020514	JP 1998-524007	19971120
KR 2000057159	A	20000915	KR 1999-704445	19990520
US 2003100525	A1	20030529	US 2002-138618	20020506
US 6800737	B2	20041005		

PRIORITY APPLN. INFO.:

US 1996-31435P	P	19961120
US 1997-975080	A	19971120
WO 1997-US21880	W	19971120
US 2000-690825	A3	20001018

AB A novel apoptosis-regulating protein termed "**Survivin**" is identified and a cDNA encoding it is cloned. The protein inhibits apoptosis and may be a target for the treatment of proliferative diseases such as **cancers** (no data) and as a tool for investigating apoptosis in normal and diseased states. The protein is abundant in **tumor** cells but is present at low levels in normal, terminally differentiated adult cells but is detectable in many fetal tissues. Aggressive **tumors** showed the highest levels of **survivins** and **survivin** levels may be a prognostic indicator for some **tumors.** Amino acid residues essential for protein function were identified by alanine scanning mutagenesis. The cloned human gene was found to include a gene on the antisense strand that encoded a protein with features typical of an apoptosis-inhibiting protein.

IT **195263-98-0**, **Survivin** (human gene **survivin**)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; **survivin**: protein that inhibits cellular apoptosis, gene encoding it and development of modulators of protein activity)

IT **195369-27-8**, DNA (human gene **survivin** plus flanks)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)

(nucleotide sequence; **survivin**: protein that inhibits cellular apoptosis, gene encoding it and development of modulators of protein activity)

L24 ANSWER 33 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:508652 HCAPLUS
DOCUMENT NUMBER: 127:232665
TITLE: A novel anti-apoptosis gene, **survivin**, expressed in **cancer** and lymphoma
AUTHOR(S): Ambrosini, Grazia; Adida, Colette; **Altieri, Dario C.**
CORPORATE SOURCE: Boyer Cent. Mol. Med., Dep. Pathol., Yale Univ. Sch. Med., New Haven, CT, 06536, USA
SOURCE: Nature Medicine (New York) (1997), 3(8), 917-921
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of programmed cell death (apoptosis) aberrantly prolonging cell viability may contribute to **cancer** by facilitating the insurgence of mutations and by promoting resistance to therapy. Despite the identification of several new apoptosis inhibitors related to bcl-2 or to the baculovirus IAP gene, it is not clear whether apoptosis inhibition plays a general role in **neoplasia.** Here, the authors described a new human gene encoding a structurally unique IAP apoptosis inhibitor, designated **survivin. Survivin** contains a single baculovirus IAP repeat and lacks a carboxyl-terminal RING finger. Present during fetal development, **survivin** is undetectable in terminally differentiated adult tissues. However, **survivin** becomes prominently expressed in transformed cell lines and in all the most common human **cancers** of lung, colon, pancreas, **prostate** and breast, in vivo. **Survivin** is also found in approx. 50% of high-grade non-Hodgkin's lymphomas (centroblastic, immunoblastic), but not in low-grade lymphomas (lymphocytic). Recombinant expression of **survivin** counteracts apoptosis of B lymphocyte precursors deprived of interleukin 3 (IL-3). These findings suggest that apoptosis inhibition may be a general feature of **neoplasia** and identify **survivin** as a potential new target for apoptosis-based therapy in **cancer** and lymphoma.

IT **195263-98-0, Survivin** (human gene **survivin**)
RL: PRP (Properties)
(amino acid sequence; sequence of anti-apoptosis gene **survivin** and expression in **cancer** and lymphoma)

IT **195369-27-8**, DNA (human gene **survivin** plus flanks)
RL: PRP (Properties)
(nucleotide sequence; sequence of anti-apoptosis gene **survivin** and expression in **cancer** and lymphoma)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> sel hit rn
E1 THROUGH E4 ASSIGNED

=> file reg
FILE 'REGISTRY' ENTERED AT 13:45:58 ON 25 JAN 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0
DICTIONARY FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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               (371761-91-0/RN)
             1 195263-98-0/BI
               (195263-98-0/RN)
             1 195369-27-8/BI
               (195369-27-8/RN)
             1 261150-38-3/BI
               (261150-38-3/RN)
L25          4 (371761-91-0/BI OR 195263-98-0/BI OR 195369-27-8/BI OR 261150-38
               -3/BI)

=> d ide can l25 tot

L25  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   371761-91-0  REGISTRY
CN   Proteinase inhibitor, survivin (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Survivin
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent
RL.P   Roles from patents:  ANST (Analytical study); BIOL (Biological study);
       PREP (Preparation); PRP (Properties); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); PREP (Preparation); PROC (Process); PRP (Properties); USES
       (Uses)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
             498 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             508 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  142:72483

REFERENCE   2:  142:69928

REFERENCE   3:  142:69773

REFERENCE   4:  142:68721

REFERENCE   5:  142:62477

REFERENCE   6:  142:54751
```

REFERENCE 7: 142:54689

REFERENCE 8: 142:53440

REFERENCE 9: 142:53410

REFERENCE 10: 142:53356

L25 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **261150-38-3** REGISTRY
CN DNA (human gene survivin promoter region-containing fragment) (9CI) (CA INDEX NAME)
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:217813

L25 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **195369-27-8** REGISTRY
CN DNA (human gene survivin plus flanks) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 10: PN: US6277640 SEQID: 10 unclaimed DNA
CN 4444: PN: WO0153836 TABLE: 3-5.claimed DNA
CN DNA (human survivin gene plus flanks)
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: PRP (Properties)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 135:314495

REFERENCE 2: 135:190437

REFERENCE 3: 129:52672

REFERENCE 4: 127:232665

L25 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **195263-98-0** REGISTRY

CN Survivin (human gene survivin) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 312: PN: WO0179449 SEQID: 586 claimed protein
CN Protein (human clone WO0179449-SEQID-6083 fragment)
CN Survivin (human)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOTECHNO, CA, CAPLUS, EMBASE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: PRP (Properties)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
4 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:98189

REFERENCE 2: 135:353783

REFERENCE 3: 129:52672

REFERENCE 4: 127:232665